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Prospective assessment after pediatric cardiac ablation: Fate of intracardiac structure and function, as assessed by serial echocardiography

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Abstract

Background—Catheter ablation puts cardiac valves at risk of damage, and children are of particular concern.

Methods—A multicenter prospective study was performed to assess the results and risks associated with radiofrequency (RF) ablation in children. Patients were aged 0 to 16 years with supraventricular tachycardia due to accessory pathway or atrioventricular node reentry, excluding patients with more than trivial congenital heart disease. A total of 481 patients were recruited into the prospective cohort and were followed up at 2, 6 and, 12 months after ablation. Complete echocardiograms were obtained before and at intervals after RF ablation, and they were reviewed by experts who were blinded with respect to diagnosis, outcome, pathway site, and study interval.

Results—Moderate valve insufficiency was quite rare (0.12%), but mild insufficiency was common, both before ablation (42.43%) and at 2 months after ablation (40.49%). Analysis of paired readings failed to demonstrate a tendency toward increased insufficiency of valves adjacent to ablation targets, with the exception of the tricuspid valve after the ablation of right freewall pathways and atrioventricular node reentry, but the degree of change was small. No clear changes in left ventricular systolic or diastolic function were observed, and dyskinesis was rare and not related to the ablation target. No intracardiac thrombosis was observed.

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Conclusions—Serious injury to cardiac valves due to RF ablation is very rare, but the tricuspid valve may be mildly affected in some cases. We identified no clear effect of RF ablation on cardiac wall motion or on left ventricular function.

Since the introduction of radiofrequency (RF) ablation, there has been concern regarding the short- and long-term safety of the procedure. Interest has been particularly focused on the potential for damage to cardiac valves, and these concerns are particularly acute in the growing and developing heart. A high rate of mitral and aortic valve damage was reported in one early, non-blinded pediatric study,¹ and such observations have influenced the methods that clinicians choose for approaching pathways in particular locations. Any assessment of the results of RF ablation with respect to the appearance of new echocardiographic abnormalities should ideally be made in a blinded fashion and with consistent expert review.

A multicenter prospective study was designed and implemented at multiple clinical pediatric electrophysiology centers (Appendix A) to assess the short- and longer-term outcomes after RF ablation in children. A complete description of the design of this study has been previously published.² A total of 481 pediatric patients were enrolled in this study. This report focuses on the results of echocardiography, with a study design that dictated preprocedure studies and blinded consistent reference-laboratory review of both pre- and postprocedure studies. The acute results of these ablation procedures, and the incidence and time course of recurrence, have been previously published.³

Methods

Patient population and recruitment

Patients recruited for the study were aged 0 to 16 years, with supraventricular tachycardia due to manifest or concealed accessory pathways or atrioventricular node reentry (AVNRT). Patients with more than trivial congenital heart disease were excluded, and all patients with Ebstein anomaly of the tricuspid valve were excluded. Patients were enrolled and studied before ablation and periodically by clinical evaluation, electrocardiogram, Holter monitor, and echocardiogram. Specifically, a complete 2-dimensional echocardiogram with color Doppler recording was obtained before the procedure and at 2 months after the ablation procedure. A copy was made onto VHS tape or on a compact disk in DICOM format.

Reference laboratory review

Copies of all echocardiogram VHS tapes or disks were forwarded by the contributing center to the data coordinating center, which batched these studies and forwarded them, with preprinted data forms, to a single echocardiography consultant (coauthor SDC) for interpretation. This consultant was blinded with respect to the patients' preablation diagnosis, pathway location, and results of ablation, as well as with respect to the interval represented by the study (ie, preablation or 2 months postablation). However, sex, age, weight, height, and body surface area were provided to allow for accurate interpretation of the studies.

A standardized data form had been previously developed for use by the echocardiography core laboratory. This form provided fields for entry of echocardiographic findings of valve insufficiency on an ordinal scale (none, mild, moderate, severe) as well as presence or absence of intracardiac thrombosis, dyskinesia of right and left ventricular (LV) freewall and septal dyskinesia, and indices of LV systolic and diastolic function.

Because the actual measurement of regurgitant volume, regurgitant fraction, or regurgitant orifice size has not been adequately reproducible in multicenter studies, we chose to focus on proximal jet width because this is routinely performed in many institutions and is technically simpler. Although the jet width does not provide a direct measure of regurgitant volume, in

this study, we were less concerned with absolute volume on regurgitation and more concerned with relative severity over serial examinations.

Statistical analysis

Summary data are reported with appropriate descriptive statistics. Substrates were categorized by diagnosis and by accessory pathway location. Because some patients had >1 arrhythmia substrate addressed by attempted ablation, we chose to use the first reported substrate as the variable for patient categorization, so that each patient is described only once. All tables reflect data summarized in this way. A reanalysis was also performed, categorizing patients by any and all substrates addressed by ablation, and in this analysis, a patient would be described several times, once for each substrate or pathway location that was addressed. Pathway locations were summarized as right freewall, right septal, left freewall, or left septal. Patients with left freewall pathways were further subcategorized based on whether the ablation attempt was made by a retrograde or an antegrade (transseptal) approach because of the variation in the need to cross the aortic valve in the latter group. All ablation procedures were included for echocardiographic analysis, whether successful or unsuccessful. Because it is common to observe mild amounts of valvar insufficiency in healthy patients, we analyzed matched pairs (eg, findings preablation vs 2 months postablation) and scored changes between the 2 time points as follows: a change toward less severe insufficiency was scored as a negative integer, and a change toward more severe insufficiency was scored as a positive integer. For example, a change from none to mild, mild to moderate, or moderate to severe would be scored as +1, whereas a change from none to moderate or mild to severe would be scored as +2, and so on for each possible combination. Intracardiac thrombosis was recorded on an ordinal scale as well (none, tiny, large), as was dyskinesia (present vs absent). For these features, a similar algorithm was used to quantify magnitude and direction of change. The images supplied for review were not always of adequate quality to allow the reviewer to make a judgment. In such cases, the data point was considered missing, but other comparisons were still possible for such echocardiograms.

The statistical significance of comparisons of the change in valvular insufficiency from baseline to 2 months between valve groups (eg, a comparison of the change in valvular insufficiency of tricuspid vs nontricuspid valves in the right septal pathway) was accomplished by categorizing change in insufficiency for each valve as either being increased or as no change/decreased and conducting a logistic regression analysis test, in which the dependent variable was an indicator of whether the valve change was for the worse, and the independent variable was an indicator of whether the valve was in the first group. Logistic regressions were performed with a “jackknifing” adjustment for clustering of observations (ie, the contribution of multiple valve data by individual patients). The jackknifing technique calculates the variance for logistic regression coefficients using the variability of regression coefficients when each individual patient is sequentially removed from the data being used in the regression, and the regression coefficients are recalculated using $N - 1$ patients, where N is the total number of patients. The statistical comparisons of changes in dyskinesia (eg, comparing changes in right ventricular (RV) dyskinesia vs the average change in septal or LV dyskinesia) were performed in the same manner. Statistical significance in the regression was assessed using the Wald χ^2 test statistic.

The protocol was approved by the institutional review board at each contributing center, and patients' families gave consent for participation in the study.

Results

The results of ablation procedures have been previously reported.⁴ Overall, of 481 patients initially enrolled in the prospective cohort, initial success was reported in 95.7% of substrates

and complications of electrophysiology study in 4.0% and of the ablation procedure in 4.2%. Average procedure time was 206.7 minutes, and the average number of RF lesions was 7.6.

Of 481 patients initially enrolled in the prospective cohort, 455 had an acceptable preprocedure echocardiogram available for review, 427 had an acceptable study from 2 months postablation available for review, and 406 had both studies available. Extensive tables that completely describe the results of these echocardiogram readings are included, for completeness, in Appendices B–E.

Valve insufficiency

In evaluating the results of unpaired analysis of readings of valve insufficiency on an ordinal scale of valve insufficiency, severe valvar insufficiency was never noted, and moderate insufficiency was very rarely present (accounting for 4/3290 [12%] readings). On the other hand, mild insufficiency was common, both in the preablation studies (720/1697 [42.43%]) and the 2 months postablation studies (645/1593 [40.49%] readings). In the baseline studies, mild insufficiency was commonly noted for the tricuspid valve (327/416 [78.61%]) and pulmonic valve (301/400 [75.25%]) but was only rarely found for the mitral (84/441 [19.05%]) and aortic valves (8/440 [1.82%]).

Considering the echocardiographic interpretations for which there were paired data, we compared the degree of insufficiency before ablation with the degree at 2 months after ablation for each valve by substrate addressed. Of 1433 comparisons, only 1 valve was judged to have changed by 2 points on the ordinal scale toward less severity, and none were judged to have changed by ≥ 2 points in the direction of greater severity. In 147 of 1433 (10.26%) comparisons, the valve insufficiency improved, and in 135 of 1433 (9.42%), it worsened by 1 point on the ordinal scale. The situation demonstrating the greatest percentage of worsening of valve insufficiency was for the tricuspid valve, specifically in left freewall pathways addressed by a retrograde approach (5/19 [26.32%]), left septal pathways (3/12 [25%]), and right freewall pathways (7/34 [20.59%]). In no other situation was the percentage of valves with worsening insufficiency as high as 20%.

To test whether catheter ablation might be responsible for some of the changes observed in valve function, we reasoned that any given catheter approach would put 1 or 2 specific valves at risk, but not others, allowing for statistical inference. For example, ablation of a left freewall pathway by the transseptal approach should normally not involve the tricuspid, pulmonic, or aortic valves but might affect the mitral valve. Such damage might be evident in comparing the incidence of increased insufficiency observed for the mitral valve with other valves, for that group of patients undergoing ablation by transseptal approach. Table I shows the comparison made, with type I error probabilities. We found that there were statistically significant differences in the profile of changes in tricuspid valve insufficiency, as compared with other valves, in patients who had ablation of AVNRT and in patients who had ablation of a right freewall pathway. Inspection of Appendix B shows that these changes are all modest, and differences in profiles between the tricuspid valve and other valves might be explainable by slight improvements in function of other valves rather than by worsening in tricuspid valve function. Changes in valve function were not significantly different in any other substrate/valve situation.

To better evaluate the effect of multiple factors on the observed changes in valve function, we performed 4 regression analyses. We performed stepwise linear regression using the following independent variables: an indicator for arrhythmia substrate addressed by ablation (AVNRT or pathway location), number of lesions that lasted <20 seconds, number of lesions that lasted >20 seconds, age, weight, fluoroscopy exposure time, and procedure time. The dependent variables were the change in tricuspid, pulmonic, mitral, or aortic valve regurgitation scores.

For tricuspid valve change, right septal pathway location was significantly associated with an increase in valve regurgitation (coefficient = -0.201 , $P = .016$), and fluoroscopy exposure time was nearly significantly associated (coefficient = 0.00173 , $P = .074$). For pulmonic valve change, the only near significant variable was age (coefficient = -0.0161 , $P = .063$). For mitral valve change, the only significant variable was the number of lesions <20 seconds (coefficient = 0.00942 , $P = .0216$). For aortic valve change, no variable was statistically significant or nearly significant.

Dyskinesia

In evaluating the results of unpaired echocardiographic readings of the degree, on an ordinal scale, of dyskinesia noted on echocardiography at baseline and 2 months after ablation, we found that dyskinesia was only rarely noted but was slightly more frequent after ablation than before ablation (0.66% vs 1.64% of measurements, not significant). The highest incidence was septal dyskinesia in patients who underwent ablation of left septal accessory pathways (2/19 [10.5%]), but the number of subjects is small.

Considering the echocardiographic interpretations for which there were paired data, we compared the degree of dyskinesia before ablation with the degree at 2 months after ablation for RV, septum, and LV by substrate addressed. Overall, dyskinesia increased in 1.69% of measurements and decreased in 0.53% of measurements.

As in valve insufficiency, we tested whether the ablation approach might be related to the dyskinetic changes observed in wall motion. We reasoned that a given catheter approach might affect one type of observed dyskinesia but not others, allowing for statistical inference. For example, ablation of a left freewall pathway by the transseptal approach might produce LV dyskinesia but not RV or septal dyskinesia. Such an effect might be evident when comparing the incidence of increased dyskinesia observed for the left freewall with RV and septum, for that group of patients undergoing ablation by transseptal approach. Table I shows the comparisons made, with type I error probabilities. We found no statistically significant increase in the incidence of dyskinesia for any of these comparisons.

Because a certain degree of wall motion abnormality may be observed in patients with preexcitation, we repeated the above analysis in a subset of the group, limiting the analysis to patients without ventricular preexcitation. Again, we found no statistically significant increase in the incidence of dyskinesia for any of these comparisons.

Thrombus

Blinded review of all echocardiograms failed to diagnose thrombus in the right atrium, RV, left atrium, or LV.

Left ventricular function

Determination of the percentage of LV fractional shortening and LV ejection fraction showed no statistically significant change in any arrhythmia substrate group. Similarly, indices of LV diastolic function (peak early mitral inflow velocity, mitral deceleration time, isovolumic relaxation time) showed no statistically significant changes in any arrhythmia substrate group.

Reanalysis for multiple substrates

The preceding analysis was conducted using the first reported substrate to categorize patients by ablated substrate. Because there were actually 535 ablated substrates in 481 patients, we repeated these analyses including all ablated substrates. Results were, in general, similar. The observation that ablation of the atrioventricular node and of right freewall pathways was associated with an increase in tricuspid valve regurgitation was true in this analysis of multiple

pathways as well. In addition, in the multiple pathway analysis alone, we found that one index of LV diastolic function worsened. Early peak mitral inflow velocity worsened in left freewall accessory pathway patients approached transeptally (paired *t* test *P* = .01), but other indices of LV diastolic function did not change, and so, the importance of this observation is questionable.

Discussion

Since the earliest applications of RF ablation for cardiac arrhythmias in the pediatric population, there has been concern about the potential for inadvertent cardiac damage as a result of these procedures. Pediatric patients' smaller size, thinner heart walls, and potentially more delicate valves suggest that complications such as acute valvar insufficiency, coronary occlusion, and cardiac perforation might be greater problems than in the adult experience. A number of single- and multicenter reports of RF ablation in children have reported the incidence of complications after procedures, and these specific problems have fortunately been rare.⁵⁻¹¹ However, in each of these series, complications were voluntarily reported, and echocardiographic examinations were not routine, nor were they usually obtained before the ablation procedure. Furthermore, indices of valve leakage are semiquantitative and subject to the potential for bias, particularly when the operator is also the reporting investigator. For these reasons, we sought to examine a large group of pediatric patients undergoing ablation at a number of pediatric centers nationally, using blinded echocardiogram interpretation by a single accomplished pediatric echocardiographer and obtaining studies both before and 2 months after ablation. By insuring that these interpretations were blinded with respect to the ablated substrate, catheter approach, and timing of the study, we are confident that we have eliminated the possibility of under- or over-reporting of valve insufficiency, which might otherwise occur when the echocardiographer has knowledge of the details of the procedure.

Echocardiography has been previously evaluated in ablation patients. An early study of 44 pediatric patients by Minich et al¹ that involved serial echocardiograms reported a 12% increase in the incidence of mitral regurgitation and a 30% increase in the incidence of aortic regurgitation after the ablation of left-sided accessory pathways by the retrograde approach. In addition to being a report of the very earliest pediatric ablation experience, this report was limited by the apparent lack of blinding of the echocardiographers with respect to diagnosis and approach. In addition, all changes were described as mild, and no statistical testing was done to determine the possibility of a type I error.

The multicenter ATAKR trial¹² included 1136 ablation procedures in 1050 patients, of whom 21% were under 21 years of age. Paired echocardiograms (preand postprocedure) were obtained in 93% of patients, and although a minor change in echocardiographic findings was reported in 135 patients, and a major change was reported in 2%, the authors could find little correlation with the specific ablation target or catheter approach. This study was limited by the lack of central echocardiography review, the lack of blinding with respect to substrate and approach, and the lack of a comprehensive statistical treatment of the echocardiographic data. In addition, no separate pediatric analysis was performed.

Other smaller series have investigated the question, with similar limitations. For example, Frias et al¹³ performed serial echocardiography in patients undergoing left-sided ablation by the retrograde route and failed to demonstrate any increased incidence of aortic insufficiency. Although this study included blinding for the echocardiogram interpretations, it is a small series. Lee and Shueller¹⁴ reported their experience with ablation in 84 children at a single center, performing serial echocardiographs without blinded interpretation, and identified no problems with valve regurgitation.

In this study, we are reassured to find quite minimal, if any, effects of ablation on cardiac valve function as well as on other indices of cardiac function. Our observation of mild changes in tricuspid valve function after right freewall ablation or ablation in AVNRT make biologic sense, given the proximity of the ablation catheter to the leaflets of the tricuspid valve, and seem real, considering that we have the same findings on both the primary analysis and reanalysis for multiple substrates. These changes, however, were, in all cases, mild and so are of questionable clinical significance.

Biologically, it is interesting that catheter ablation can be performed with the delivery of destructive energy to the heart near the cardiac valves with little identifiable consequence for subsequent valve function. From the earliest days of RF ablation experiments in animals, the relative lack of direct observable thermal injury to the valve leaflets has been notable.^{15,16} The biophysical properties of these tissues that provide relative protection during RF energy delivery are unknown, but one may speculate that leaflet tissue presents a relatively higher impedance to the passage of RF current as compared with the nearby myocardium, and so, resistive heating occurs in the myocardium. Furthermore, there may well be barriers to convective heat transmission from the nearby heated myocardium.

The lack of any clear effect of RF ablation on cardiac wall motion or on LV function suggests that significant, clinically apparent coronary injury is not likely to be common. Clinically silent coronary injury is, of course, not ruled out by this method. Several recent reports of acute coronary injury have appeared,^{17,18} and in one of these cases, echocardiography was normal.¹⁷ A true assessment of the impact on coronary arterial structure and function in smaller hearts will require selective angiography or cardiac perfusion studies, perhaps evaluating coronary reserve by exercise or pharmacologic stress testing.

We considered, as well, whether the slight increase in tricuspid valve regurgitation after right freewall pathway ablation and ablation for AVNRT might be related to worsening of dyskinesis, leading in turn to valve dysfunction. However, none of the patients with AVNRT had a change in dyskinesis status. Furthermore, for freewall pathway, ablation along the tricuspid annulus is no more likely to lead to dyskinesis than along the mitral annulus, and so, we do not consider changes in ventricular wall motion to be an important contributor to the changes observed in this study.

We are disappointed by our inability to obtain echocardiographic follow-up closer to 100% in this clinical study group. In contrast, clinical follow-up at this interval was much better, 96.7%, as previously reported,³ and most of this loss of echocardiographic material was due to technical issues with the echocardiographic recording rather than actual failure to obtain the echocardiogram. In designing this study, we realized that technical standardization would be difficult across multiple contributing centers, and so, we initially considered limiting the study to 4 or 5 centers, which would undergo on-site training. However, based on prior registry data, we realized that to recruit a sufficient sample size, we needed to open the study to many centers. This, in turn, meant that on-site training of all centers would be prohibitively expensive.

We considered the possibility that valvar dysfunction might be disproportionately represented in our group that did not get their scheduled echocardiogram at 2 months or had an incomplete study, thereby introducing bias. We view this as unlikely, however: it seems much more likely that patients with significant valve disease would be continuing in follow-up because they would have heart murmurs and would be getting clinically indicated echocardiograms, and such studies would be naturally more extensive and less likely to be judged unacceptable.

In conclusion, our study has identified little or no evidence for serious, previously unappreciated, injury to cardiac valves as a result of the application of RF energy in the course of transcatheter ablation. In addition, there seems to be no clear effect of RF ablation on cardiac

wall motion or on LV function. Although acute coronary injury is conceivable, and valves may be disrupted by direct catheter trauma, it seems likely that such events are and will continue to be rare.

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Appendix A. Participants and Contributing Centers

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Table I
Summary of statistical comparisons for valve insufficiency and dyskinesia

Substrate	Valve insufficiency		Dyskinesia	
	Increased versus no change or decreased		Increased versus no change or decreased	
	Comparison	Wald χ^2 , <i>P</i>	Comparison	Wald χ^2 , <i>P</i>
Right freewall pathway	Tricuspid versus others	<01	RV dyskinesia versus septal or LV dyskinesia	NS
Right septal pathway	Tricuspid versus others	NS	Septal or RV dyskinesia versus LV dyskinesia	NS
Left freewall pathway, transseptal	Mitral versus others	NS	LV dyskinesia versus septal or RV dyskinesia	NS
Left freewall pathway, retrograde	Aortic or mitral versus others	NS	LV dyskinesia versus septal or RV dyskinesia	NS
Left septal pathway	Aortic or mitral versus others	NS	Septal or LV dyskinesia versus RV dyskinesia	NS
AVNRT	Tricuspid versus others	<01	Septal or RV dyskinesia versus LV dyskinesia	NS

NS, Not significant.

Appendix B.1. Part 1

Vascular Insufficiency at Baseline and Two Months By Substrate

Substrate	Severity	Tricuspid				Pulmonic				Mitral			
		Baseline		2 m		Baseline		2 m		Baseline		2 m	
		n	%	n	%	n	%	n	%	n	%	n	%
Right free wall pathway	None	13	28.26	6	15.38	8	18.60	12	29.27	40	83.33	39	86.67
	Mild	33	71.74	33	84.62	35	81.40	29	70.73	8	16.67	6	13.33
	Moderate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Right septal pathway	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	None	9	14.75	15	27.27	18	30.51	17	35.42	51	82.26	46	82.14
	Mild	51	83.61	40	72.73	41	69.49	31	64.58	10	16.13	10	17.86
Left free wall pathway, transseptal	Moderate	1	1.64	0	0.00	0	0.00	0	0.00	1	1.61	0	0.00
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	None	30	18.63	27	17.53	38	24.68	42	28.57	130	76.47	136	81.44
Left free wall pathway, retrograde	Mild	131	81.37	127	82.47	116	75.32	105	71.43	40	23.53	31	18.56
	Moderate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Left freewall pathway, retrograde	None	9	42.86	6	26.09	6	30.00	7	35.00	22	91.67	22	88.00
	Mild	12	57.14	17	73.91	14	70.00	13	65.00	2	8.33	3	12.00
	Moderate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Left septal pathway	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	None	4	33.33	5	29.41	3	25.00	5	29.41	13	81.25	15	83.33
	Mild	8	66.67	12	70.59	9	75.00	12	70.59	3	18.75	3	16.67
AVNRT	Moderate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	None	23	20.00	14	13.86	26	23.21	27	27.84	100	82.64	94	87.85
Substrate summary	Mild	92	80.00	86	85.15	86	76.79	69	71.13	21	17.36	13	12.15
	Moderate	0	0.00	1	0.99	0	0.00	1	1.03	0	0.00	0	0.00
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Substrate summary	None	88	21.15	73	17.55	99	24.75	110	27.50	356	80.73	352	79.82
	Mild	327	78.61	315	75.72	301	75.25	259	64.75	84	19.05	66	14.97
	Moderate	1	0.24	1	0.24	0	0.00	1	0.25	1	0.23	0	0.00
Severe	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Appendix B.2. Part 2

Vascular Insufficiency at Baseline and Two Months By Substrate

Substrate	Severity	Aortic						Valve summary					
		Baseline			2 m			Baseline			2 m		
		n	%	n	n	%	%	n	%	n	n	%	%
Right freewall pathway	None	46	97.87	45	100.00	107	58.15	102	60.00	209	59.04		
	Mild	1	2.13	0	0.00	77	41.85	68	40.00	145	40.96		
	Moderate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
Right septal pathway	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
	None	62	100.00	55	100.00	140	57.38	133	62.15	273	59.61		
	Mild	0	0.00	0	0.00	102	41.80	81	37.85	183	39.96		
Left freewall pathway, transseptal	Moderate	0	0.00	0	0.00	2	0.82	0	0.00	2	0.44		
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
	None	166	97.08	163	97.60	364	55.49	368	57.95	732	56.70		
Left freewall pathway, retrograde	Mild	5	2.92	4	2.40	292	44.51	267	42.05	559	43.30		
	Moderate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
Left septal pathway	None	24	100.00	25	100.00	61	68.54	60	64.52	121	66.48		
	Mild	0	0.00	0	0.00	28	31.46	33	35.48	61	33.52		
	Moderate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
AVNRT	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
	None	16	100.00	18	100.00	36	64.29	43	61.43	79	62.70		
	Mild	0	0.00	0	0.00	20	35.71	27	38.57	47	37.30		
Substrate summary statistics	Moderate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
	None	118	98.33	105	99.06	267	57.05	240	58.39	507	57.68		
	Mild	2	1.67	1	0.94	201	42.95	169	41.12	370	42.09		
	Moderate	0	0.00	0	0.00	0	0.00	2	0.49	2	0.23		
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		
	None	432	98.18	411	93.41	975	57.45	946	59.38	1921	58.39		
	Mild	8	1.82	5	1.14	720	42.43	645	40.49	1365	41.49		
	Moderate	0	0.00	0	0.00	2	0.12	2	0.13	4	0.12		
	Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00		

Appendix C

Change in valvular insufficiency at 2 months relative to baseline

Substrate	Change in insufficiency	Tricuspid		Pulmonic		Mitral		Aortic		Valve summary	
		n	%	n	%	n	%	n	%	n	%
Right freewall pathway	Less severe (-2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Less severe (-1)	2	5.88	5	15.63	3	7.69	1	7.69	11	7.69
	No change (0)	25	73.53	25	78.13	34	87.18	37	87.18	121	84.62
	More severe (+1)	7	20.59	2	6.25	2	5.13	2	5.13	11	7.69
	More severe (+2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Right septal pathway	Less severe (-2)	0	0.00	0	0.00	1	1.92	0	0.00	1	0.51
	Less severe (-1)	13	25.00	9	21.43	3	5.77	0	0.00	25	12.63
	No change (0)	33	63.46	28	66.67	43	82.69	52	100.00	156	78.79
	More severe (+1)	6	11.54	5	11.90	5	9.62	0	0.00	16	8.08
	More severe (+2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Left freewall pathway, transseptal	Less severe (-2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Less severe (-1)	16	11.27	24	19.20	22	14.01	2	1.27	64	11.00
	No change (0)	106	74.65	81	64.80	120	76.43	155	98.10	462	79.38
	More severe (+1)	20	14.08	20	16.00	15	9.55	1	0.63	56	9.62
	More severe (+2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Left freewall pathway, retrograde	Less severe (-2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Less severe (-1)	2	10.53	4	26.67	2	9.09	0	0.00	8	10.26
	No change (0)	12	63.16	10	66.67	17	77.27	22	100.00	61	78.21
	More severe (+1)	5	26.32	1	6.67	3	13.64	0	0.00	9	11.54
	More severe (+2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Left septal pathway	Less severe (-2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Less severe (-1)	3	25.00	2	18.18	2	12.50	0	0.00	7	12.73
	No change (0)	6	50.00	7	63.64	12	75.00	16	100.00	41	74.55
	More severe (+1)	3	25.00	2	18.18	2	12.50	0	0.00	7	12.73
	More severe (+2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
AVNRT	Less severe (-2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Less severe (-1)	8	8.89	14	16.47	9	8.82	1	1.00	32	8.49
	No change (0)	66	73.33	56	65.88	89	87.25	98	98.00	309	81.96
	More severe (+1)	16	17.78	15	17.65	4	3.92	1	1.00	36	9.55
	More severe (+2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Substrate summary	Less severe (-2)	0	0.00	0	0.00	1	0.26	0	0.00	1	0.07
	Less severe (-1)	44	12.61	58	18.71	41	10.57	4	1.04	147	10.26
	No change (0)	248	71.06	207	66.77	315	81.19	380	98.45	1150	80.25
	More severe (+1)	57	16.33	45	14.52	31	7.99	2	0.52	135	9.42
	More severe (+2)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Appendix D.1. Part 1**Dyskinesia at Baseline and Two Months by Substrate**

Substrate	Dyskinesia	RV dyskinesia				Septal dyskinesia			
		Baseline		2 m		Baseline		2 m	
		n	%	n	%	n	%	n	%
Right freewall pathway	Present	0	0.0	0	0.0	3	6.1	2	4.3
	Absent	29	59.2	29	63.0	46	93.9	41	89.1
	N/A	20	40.8	17	37.0	0	0.0	3	6.5
Right septal pathway	Present	0	0.0	0	0.0	4	6.2	2	3.4
	Absent	48	73.8	36	61.0	59	90.8	55	93.2
	N/A	17	26.2	23	39.0	2	3.1	2	3.4
Left freewall pathway, transseptal	Present	0	0.0	2	1.2	1	0.6	4	2.4
	Absent	112	64.7	113	66.9	164	94.8	164	97.0
	N/A	61	35.3	54	32.0	8	4.6	1	0.6
Left freewall pathway, retrograde	Present	0	0.0	0	0.0	0	0.0	0	0.0
	Absent	13	46.4	15	57.7	25	89.3	25	96.2
	N/A	15	53.6	11	42.3	3	10.7	1	3.8
Left septal pathway	Present	0	0.0	1	5.3	0	0.0	2	10.5
	Absent	9	56.3	10	52.6	14	87.5	16	84.2
	N/A	7	43.8	8	42.1	2	12.5	1	5.3
AVNRT	Present	0	0.0	0	0.0	0	0.0	0	0.0
	Absent	92	74.2	72	66.7	120	96.8	105	97.2
	N/A	32	25.8	36	33.3	4	3.2	3	2.8
Substrate summary	Present	0	0.00	3	0.70	8	1.76	10	2.34
	Absent	303	66.59	275	64.40	428	94.07	406	95.08
	N/A	152	33.41	149	34.89	19	4.18	11	2.58

Appendix D.2. Part 2

Substrate	Dyskinesia	LV dyskinesia				All dyskinesia locations			
		Baseline		2 m		Baseline		2 m	
		n	%	n	%	n	%	n	%
Right freewall pathway	Present	0	0.0	1	2.2	3	2.0	3	2.2
	Absent	49	100.0	42	91.3	124	84.4	112	81.2
	N/A	0	0.0	3	6.5	20	13.6	23	16.7
Right septal pathway	Present	0	0.0	0	0.0	4	2.1	2	1.1
	Absent	63	96.9	57	96.6	170	87.2	148	83.6
	N/A	2	3.1	2	3.4	21	10.8	27	15.3
Left freewall pathway, transseptal	Present	0	0.0	4	2.4	1	0.2	10	2.0
	Absent	166	96.0	164	97.0	442	85.2	441	87.0
	N/A	7	4.0	1	0.6	76	14.6	56	11.0
Left freewall pathway, retrograde	Present	0	0.0	0	0.0	0	0.0	0	0.0
	Absent	25	51.0	25	96.2	63	75.0	65	83.3
	N/A	3	6.1	1	3.8	21	25.0	13	16.7
Left septal pathway	Present	1	6.3	3	15.8	1	2.1	6	10.5
	Absent	14	87.5	15	78.9	37	77.1	41	71.9
	N/A	1	6.3	1	5.3	10	20.8	10	17.5
AVNRT	Present	0	0.0	0	0.0	0	0.0	0	0.0
	Absent	120	96.8	105	97.2	332	89.2	282	87.0
	N/A	4	3.2	3	2.8	40	10.8	42	13.0
Substrate summary	Present	1		8	1.87	9	0.66	21	1.64
			0.22						
	Absent	437		408	95.55	1168	85.57	1089	85.01
			96.04						
	N/A	17		11	2.58	188	13.77	171	13.35
			3.74						

Appendix E

Dyskinesia Change from Baseline to 2 Months

Substrate	Dyskinesia change	RV dyskinesia		Septal dyskinesia		LV dyskinesia		All dyskinesia locations	
		n	%	n	%	n	%	n	%
Right freewall pathway	Decreased	0	0.0	2	5.3	0	0.0	2	2.2
	No change	16	100.0	34	89.5	37	97.4	87	94.6
	Increased	0	0.0	2	5.3	1	2.6	3	3.3
Right septal pathway	Decreased	0	0.0	2	3.7	0	0.0	2	1.5
	No change	26	100.0	51	94.4	54	100.0	131	97.8
	Increased	0	0.0	1	1.9	0	0.0	1	0.7
Left freewall pathway, transseptal	Decreased	0	0.0	1	0.6	0	0.0	1	0.3
	No change	78	98.7	150	97.4	152	98.1	380	97.9
	Increased	1	1.3	3	1.9	3	1.9	7	1.8
Left freewall pathway, retrograde	Decreased	0	0.0	0	0.0	0	0.0	0	0.0
	No change	7	100.0	22	100.0	22	100.0	51	100.0
	Increased	0	0.0	0	0.0	0	0.0	0	0.0
Left septal pathway	Decreased	0	0.0	0	0.0	0	0.0	0	0.0
	No change	5	83.3	12	85.7	13	86.7	30	85.7
	Increased	1	16.7	2	14.3	2	13.3	5	14.3
AVNRT	Decreased	0	0.0	0	0.0	0	0.0	0	0.0
	No change	47	100.0	99	100.0	99	100.0	245	100.0
	Increased	0	0.0	0	0.0	0	0.0	0	0.0
Substrate summary	Decreased	0		5		0		5	
	No change	179	0.00	368	1.31	377	0.00	924	0.53
	Increased	2	98.90	8	96.59	6	98.43	16	97.78
			1.10		2.10		1.57		1.69